REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1-20, 24-59, and 65-67 have been canceled. Claims 60 and 64 have been amended, and new claims 68-97 have been added. Therefore, claims 21-23, 60-64, and 68-97 are currently pending. Reconsideration of the pending application is respectfully requested.

The 35 U.S.C. §112 Rejections

Claims 21-23 stand rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserted that those claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Examiner stated that the claims encompass targeting any nucleic acid in a teleost embryo using any polynucleotide analogue. The Examiner asserted that the specification does not disclose which target nucleic acids are present in the embryo. According to the Examiner, without a clear indication of which nucleic acids are present in the embryo, one of skill in the art would not be able to design the polynucleotide analogues and would not be able to reduce the expression of the target nucleic acid. The Examiner concluded that considering all of the nucleic acids which are expressed during teleost embryonic development, the specification has not adequately described a sufficient number of target nucleic acids or polynucleotide analogues.

Contrary to the Examiner's assertion, the specification exemplifies the methods of claims 21-23 using more than a sufficient number of target nucleic acids and polynucleotide analogues. For example, Applicants examined the distribution within the embryo of a morpholino oligonucleotide (MO), a 3'-5' phosphoroamidate oligonucleotide, a 2'-O methyl RNA oligonucleotide, and 2 different peptide nucleic acids (PNAs). In addition, Applicants exemplified reduced expression using 21 different polynucleotide analogues, both MOs and

The 12 selected nucleic acids are representative of the claimed genus of nucleic acids in a teleost embryo because the selected nucleic acids include a number of different types of genes (e.g., a transcription factor, a membrane-bound receptor, a secreted ligand, and an enzyme involved in heme biosynthesis), and because the selected nucleic acids are expressed in different embryonic tissues and at different times during embryogenesis. Similarly, the polynucleotide analogues exemplifed are representative of the claimed genus because the polynucleotide analogues exemplified include MOs, PNAs, 3'-5' phosphoroamidate oligonucleotides, and 2'-O methyl RNA oligonucleotides, and are directed to a variety of positions within the selected nucleic acid (e.g., 5' untranslated regions (UTR) or regions flanking and including the sequence encoding the initiating methionine). In addition, the polynucleotide analogues exemplified are representative of the genus of polynucleotide analogues because, for example, the backbones of the exemplified oligonucleotide are entirely different from one another and have no common structural features other than the nucleoside bases. Given that Applicants observed uniform distribution using different polynucleotide analogues, and further achieved reduced expression of a number of selected nucleic acids using different polynucleotide analogues, Applicants submit that the level of skill and knowledge in this art is high.

According to the Written Description Guidelines, a claimed genus can be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. According to the Written Description Guidelines, a "representative number of species" means that the species which are adequately described are representative of the entire genus, and what constitutes a "representative number" is an inverse function of the level of skill and knowledge in the art. The Written Description Guidelines indicate that the description need not provide individual support for each species that the genus embraces. The Written Description Guidelines further indicate that the description need only describe in detail that which is new or not conventional.

Given the high level of skill and knowledge in this art, as well as the reduction to practice of more than a representative number of species, Applicants have met the written description

Claims 21-23 also stand rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserted that those claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner indicated that the claims encompass a large number of target nucleic acids and a large number of polynucleotide analogues, and asserted that the specification has not adequately described a sufficient number of these molecules. According to the Examiner, without a clear indication of which nucleic acids are expressed in the developing teleost embryo, one of skill in the art would not known how to make and use the invention without performing an undue amount of additional experimentation. The Examiner further asserted that one of skill in the art would not know which polynucleotide analogues could be used without performing an undue amount of additional experimentation.

Applicants' specification does, in fact, adequately describe a sufficient number of selected nucleic acids and a sufficient number of polynucleotide analogues to enable claims 21-23. As discussed above, the specification describes reduced expression of 12 different selected nucleic acids using 21 different polynucleotide analogues including both MOs as well as PNAs. The specification also describes uniform distribution in the embryo of 5 different polynucleotide analogues, including MOs, PNAs, 3'-5' phosphoroamidate oligonucleotides, and 2'-O methyl RNA oligonucleotides.

In addition, a person of ordinary skill in the art can utilize the literature and sequence databases or recombinant nucleic acid libraries to identify additional nucleic acids that are expressed in a teleost embryo. For example, the sequence of the zebrafish genome is known and available in public databases maintained by the National Center for Biotechnology Information (NCBI) and the Wellcome Trust Sanger Institute. In addition, the specification at pages 9-11 and Example 3 teaches how to design suitable polynucleotide analogues. Once a selected sequence is identified and a polynucleotide analogue designed, the specification teaches those of skill in the art how to evaluate a polynucleotide analogue for the ability to reduce expression of the

Applicants provide a significant amount of direction and guidance in the form of a large number of working examples. Given that Applicants observed some degree of reduced expression of the selected nucleic acid with almost all of the 21 polynucleotide analogues exemplified, a person of ordinary skill would not need to screen undue numbers of polynucleotide analogues to identify those molecules falling within the scope of the claims. In addition, the experimental steps required to practice the claimed invention are routinely performed in the laboratory, and therefore, practicing the claimed methods would not require undue experimentation. Claims 21-23 are enabled, and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 59-64 stand rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserted that those claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner indicated that the claims encompass any two polynucleotides which are complementary to different regions of any target nucleic acid and which have a synergistic effect when used together. The Examiner asserted, however, that the specification has not identified how to design and make synergistic antisense polynucleotides to any target nucleic acid of interest. The Examiner further asserted that here is no indication which regions of any target nucleic acid can be targeted by polynucleotide analogues and consistently result in a synergistic inhibition of target gene expression.

Applicants have canceled claim 59 without prejudice to continued prosecution, and amended claim 60 to be an independent claim. With respect to claims 60-64, the specification exemplifies the methods of claims 60-64 using 3 different pairs of polynucleotide analogues with each pair directed to a different selected nucleic acid. See Examples 3, 18, 24, and 25. In each case, a synergistic reduction in expression of the selected nucleic acid was observed. Applicants' specification discloses how to make polynucleotide analogues, and how to test polynucleotide

the selected nucleic acids include different types of genes, and because the selected nucleic acids are expressed in different tissues and at different embryonic developmental times. Similarly, the polynucleotide analogues exemplifed are representative of the claimed genus because the polynucleotide analogues exemplified are directed to a variety of positions within the selected nucleic acid (e.g., 5' untranslated regions (UTR) or regions flanking and including the sequence encoding the initiating methionine). Given that Applicants observed a synergistic reduction in expression with each of the three pairs of polynucleotide analogues exemplified, Applicants submit that the level of skill and knowledge in this art is high.

The Written Description Guidelines were discussed above with respect to the rejection of claims 21-23. With respect to claims 60-64, Applicants reduced to practice 3 different species of the claimed genus of selected nucleic acids and 3 different species of the claimed genus of polynucleotide analogues. Given the high level of skill and knowledge in this art, as well as the reduction to practice of a representative number of species, Applicants have met the written description requirement. Applicants submit that the rejection of claim 59 is moot, and respectfully request that the rejection of claims 60-64 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 59-64 also stand rejected under 35 U.S.C §112, first paragraph, as the Examiner asserted that those claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner asserted that the claims potentially encompass millions of different polynucleotide analogues, and that the specification has not sufficiently described the polynucleotide analogues which would have synergistic activity, nor has the specification disclosed how to design and make the synergistic polynucleotide analogues specific for every possible target nucleic acid molecule. The Examiner asserted that without a sufficient description of molecules encompassed by the claims, one of skill in the art would not know how to make or use the invention without performing an undue amount of additional experimentation.

Applicants' specification does, in fact, adequately describe a reduction in expression of a sufficient number of selected nucleic acids using a sufficient number of polynucleotide analogues to enable claims 60-64. The specification describes a synergistic reduction in expression of 3 different pairs of polynucleotide analogues directed to 3 different selected nucleic acids. As discussed above, the skills required to identify a selected nucleic acid sequence, design at least two polynucleotide analogues, and evaluate the polynucleotide analogues for their ability to reduce expression of the selected nucleic acid, are well within the purvue of those of ordinary skill in the art. Furthermore, the specification provides additional guidance on designing and using pairs of polynucleotide analogues. See, for example, pages 14-16.

Applicants provide a significant amount of direction and guidance in the form of working examples and disclosure in the specification. Given that Applicants observed a synergistic reduction in expression of all 3 of the selected nucleic acids exemplified, a person of ordinary skill would not need to screen undue numbers of polyncucleotide analogues to identify those molecules falling within the scope of the claims. In addition, the experimental steps required to practice the claimed methods are routinely performed in the laboratory, and therefore, practicing the claimed methods would not require undue experimentation.

In view of the above remarks, Applicants submit that the rejection of claim 59 is moot, and respectfully request that the rejection of claims 60-64 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102 Rejections

Claims 21-23 stand rejected under 35 U.S.C. §102(b) as being anticipated by Barabino et al. (*Mech. Develop.*, 1997, 63:133-143. This rejection is respectfully traversed.

The Examiner asserted that Barabino teaches a method for producing a teleost embyro comprising a polynucleotide analogue, wherein the teleost embryo is a zebrafish embryo and wherein the polynucleotide analogue is present in an amount effective to reduce expression of a target nucleic acid in the embryo, by contacting the embryo with the polynucleotide.

example, section 4.3 on page 142 of Barabino. According to the present invention, polynucleotide analogues are chemically modified polynucleotides. See, for example, page 9, line 25. The 2'-deoxyoligonucleotides of Barabino are not polynucleotide analogues, and Barabino does not teach that polynucleotide analogues can be used to reduce expression of selected nucleic acids in a teleost embryo.

Therefore, Barabino does not anticipate the invention of claims 21-23, and Applicants respectfully request that the rejection of claims 21-23 under 35 U.S.C. §102(b) be withdrawn.

Claim 59 stands rejected under 35 U.S.C. §102(b) as being anticipated by Reed (U.S. Patent No. 5,734,033). Without acquiescing to the Examiner's rejection, Applicants have canceled claim 59 without prejudice to continued prosecution, and amended claim 60 to be an independent claim. Therefore, Applicants respectfully submit that the rejection of claims 59 under 35 U.S.C. §102(b) is moot.

The 35 U.S.C. §103 Rejections

Claims 59 and 64 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Reed (U.S. Patent No. 5,734,033) in view of Summerton et al. (*Antisense & Nucl. Acid Drug Develop.*, 1997, 7:187-195). Without acquiescing to the Examiner's rejection, Applicants have canceled claim 59 and amended claim 60 to be an independent claim. Applicants also have amended claim 64 to depend from claim 60. Therefore, Applicants respectfully submit that the rejection of claims 59 and 64 under 35 U.S.C. §103(a) is moot.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that claims 21-23, 60-64, and 68-97 are in condition for allowance, which action is respectfully requested. Enclosed is a $465 check for the Petition for Three-Month Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: September 11, 2003

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